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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621

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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/766,642	ATALA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12,14-26 and 28-33* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12,23-26,28,29 and 33* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 28 November 2006 has been received and entered into the application file. Claims 1-4, 6-10, 12 and 14-33 remain pending in the current application, with claims 14-22 and 30-32 being withdrawn from consideration as being directed to non-elected inventions. The amendments to claims 1, 2, 6-10 and 23 have been entered. Claim 27 has been cancelled. Claims 1-4, 6-10, 12, 23-29 and 33 have been considered on the merits.

Response to Arguments

Applicants' arguments, received in the response of 28 November 2006, have been fully considered, and are found persuasive in part. Each of the arguments will be addressed below, as appropriate. Rejections/objections not repeated in this action have been withdrawn.

Regarding the rejection of claims 1-4, 6-10, 12, 23-29 and 33 under 35 USC 112, second paragraph, the amendments to the claims have obviated the reasons for rejection.

Regarding the rejection of claims 1-4, 6-10, 12, 23-29 and 33 under 35 USC 103(a), applicants argue that the combination of references do not teach or suggest the claims, as amended. Specifically, applicants argue that Naughton et al does not teach or suggest using an injectable polymer, but rather implants a three-dimensional framework; furthermore, while Naughton et al teaches use of genetically manipulated cells, they do not teach or suggest use of *transiently transfected* cells. Applicants argue there is not proper motivation to modify the method of Naughton et al in view of the other teachings because Naughton et al does not recognize any deficiencies or shortcomings of their method. Applicants further

argue that because Naughton et al teaches the genetically manipulated cells provide *sustained* release of the transfection products, this constitutes a teaching away from the use of *transiently transfected* cells.

In response to the argument that Naughton et al uses a three-dimensional framework and not an injectable polymer matrix, it is initially noted that only claim 1 and dependents thereof now recite such a limitation, claim 23 and dependents thereof are not so limited. However, a new grounds of rejection has been made to address this new limitation.

In response to the argument that there is not proper motivation to modify the teachings of Naughton et al in view of the other references because Naughton et al does not recognize any deficiencies or shortcomings with their method, it is noted that motivation to modify a teaching need not come directly from the *primary* reference, but rather can be found within *any* of the cited references, *or* in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case each of Penn et al and Lu et al provide motivation for making the suggested modifications to the method of Naughton et al. For example, regarding the modification to use transiently transfected cells in place of stably transfected cells, Penn et al specifically teach local and transient expression of VEGF is sufficient to induce neovascularization *while minimizing systemic effects and hemangioma formation* (See Penn et al, Pg. 1, paragraph 0004); potential systemic effects and hemangioma formation are potential drawbacks to using stably transfected cells, in light of this one would be motivated to use transiently transfected cells, as taught by Penn et al. Regarding the modification to use myoblasts as the specific type of 'heart tissue' cell, it is noted Naughton et al specifically teach use of heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). Lu et al was referenced to show that, at the time the invention was made, it was well known that use of myoblasts were commonly used in the formation of bioartificial muscles; therefore, based on the knowledge generally available in the art (as evidenced by Lu et al), one would have been motivated to

specifically use myoblasts as the type of heart cells in the method of Naughton et al to reconstruct heart muscle.

Finally, in response to applicants' argument that Naughton et al teaches away from using transiently transfected cells because they use stably transfected cells, it is pointed out that it has been held that a reference merely not teaching every limitation does not constitute teaching away by that reference. See *In re Grasselli* 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983).

In response to the rejection of claims 23, 25, 26, 29 and 33 under 35 USC 103(a) over Meana et al in view of Andree et al, applicants argue the amended claims now require at least one of the cell populations to be myoblasts, such a limitation is not taught or suggested by the cited references which deal with reconstruction of skin tissue (fibroblasts and keratinocytes). This is persuasive, the rejection of record is withdrawn.

Claim Objections

Claim 1 is objected to because of the following informalities:

Amended claim 1 is slightly awkward; however, the language is not so unclear as to render the claim indefinite. Specifically, because the claim requires selection of first and second cell populations that each come from different sources (e.g. are not the same cell type), it can be considered confusing to recite a 'general' cell population in the first step (transiently transfecting *cells*) as this suggests the subsequently mentioned cell populations are derived from this one cell population. It would be remedial to change the language to combine the first and second steps of the method, as follows:

"A method of organ augmentation comprising the steps of:

transiently transfecting a first population of cells with a plasmid encoding the angiogenesis modulating agent VEGF;

selecting a second population of cells, wherein the second population of cells comprises cells of a different cell type than the first population;

suspending the first population of cells and the second population of cells...."

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-10, 12, 23-26, 28-29 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al, (US 2003/0007954), in view of Lu et al (Circulation, 2001), Atala (US Patent 6,479,064) and MacLaughlin et al (US Patent 6,692,738), and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

Applicants amended claim 1 is directed to a method of organ augmentation comprising transiently transfecting a first population of cells with a plasmid encoding angiogenesis modulating agent VEGF; selecting a second population of cells, wherein the second population of cells comprises cells of a different cell type than the first population; suspending the first and second population of cells in an injectable polymer matrix; injecting the polymer matrix into a target tissue region where the first population of cells will express the VEGF; thereby inducing assimilation and differentiation of at least one of the populations of cells in the target region and augmenting organ function. Claim 2 requires the transiently transfected cells to produce the angiogenesis modulating agent for less than three weeks. Claim 3 requires the first population of cells to comprise undifferentiated cells. Claim 4 requires the first

population of cells to comprise vascular endothelial cells. Claim 6 requires the second population of cells to comprise undifferentiated cells. Claim 7 requires the second population of cells to comprise vascular endothelial cells. Claim 8 requires the polymer matrix to comprise collagen; claim 8 requires the collagen to be type I collagen. Claim 10 requires first population of cells to express the angiogenesis modulating agent for less than about 10 weeks. Claim 12 requires the first population of cells to comprise myoblasts.

Applicant's amended claim 23 is directed to a method for augmenting organ function, comprising culturing at least a first population of cells on a matrix material to produce an organ construct; transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells comprises cells of a different cell type than the first population, and wherein either the first or second population of cells comprises myoblasts; and implanting the organ construct and the transfected cells *in vivo* at one target site to replace or augment organ function; wherein the transfected cells express the angiogenesis modulating agent for less than about 3 weeks. Claim 24 requires the matrix to be decellularized tissue. Claim 25 requires the matrix to be a hydrogel. Claim 26 requires the matrix to be a polymer. Claim 28 requires the angiogenesis modulating agent to be VEGF. Claim 29 requires the method to further comprise assimilating the transfected cells into a tissue layer. Claim 33 requires the organ construct and the transfected cells to be implanted at a plurality of target sites *in vivo.*

Naughton et al teach a method for treatment of ischemic tissue, particularly myocardial ischemia, by producing and implanting a three-dimensional stromal tissue construct to the ischemic region of the heart to promote vascularization of the heart and regeneration of the damaged cardiac muscle cells (which applicant calls organ augmentation) (See Naughton et al, Pg. 2, paragraph 0028). The method of Naughton et al comprises formation of a three-dimensional stromal tissue construct by inoculating

stromal cells onto a three-dimensional scaffold; and then implantation of the three-dimensional tissue construct at various locations where the heart tissue was damaged by ischemia so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057). It would further have been obvious to one of ordinary skill in the art, at the time the invention was made, to implant multiple tissue constructs at multiple sites, as needed to correct ischemic damage. One would be motivated to produce and implant as many tissue constructs as needed to correct all areas of ischemic damage in order to fully treat a patient.

Regarding the material of the three-dimensional scaffold (matrix), Naughton et al teach the three-dimensional scaffold can consist of PGA, collagen, polylactic acid (a polymer) or hyaluronic acid (See Naughton et al, Pg. 2, paragraph 0032). It is noted that Naughton et al makes use of a 3-D framework as the scaffold/matrix material; however, at the time the invention was made it was well known that various substrate materials and forms could be successfully utilized for delivery of cells to a target tissue region for assimilation into the target tissue. In support, MacLaughlin et al and Atala et al are referenced. MacLaughlin et al discusses the three main types of matrices: microfabricated devices, fibrous scaffolds (such as that of Naughton et al), and injectable hydrogels; more specifically, with regards to hydrogels, MacLaughlin et al disclose various polymeric materials, including collagen, which are used as the injectable hydrogel materials (See MacLaughlin et al, abstract & col. 7-14). Similarly, Atala et al also disclose various matrix materials and forms which are commonly used in the field of tissue engineering and cell delivery, including hydrogels and decellularized tissue (See, e.g. Atala, Pg. 1, paragraph 0012). Therefore, at the time the invention was made different matrix material and forms were recognized as functional equivalents for delivery of cells to the body for purposes of tissue engineering; thus, though Naughton et al utilize scaffold frameworks, it would have been obvious to the skilled artisan to alternatively use injectable polymeric hydrogels, including type I collagen, or decellularized tissue, as the matrix material for culture and delivery of the cells. This grounds of rejection (substitution of a known

equivalent for one taught in a reference) is deemed proper, because the functional equivalence of the different matrix materials is taught in the prior art- not in applicants disclosure. *In re Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980).

Regarding the types of cells cultured on the three-dimensional scaffold Naughton et al teach the stromal cell populations can comprise fibroblasts as well as tissue specific cells, such as heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). It would have been obvious to one of ordinary skill in the art to more particularly use myoblasts (which are considered undifferentiated cells). Myoblasts are commonly used in the formation of bioartificial muscles (See, e.g. Lu et al, Pg. 595, col. 1) and thus one of ordinary skill in the art would have been motivated to use these precursor cells (undifferentiated cells) as the specific heart cells in the tissue construct of Naughton et al in order to allow for natural differentiation and formation of the cardiac tissues. One would have expected success using myoblasts because their use in bioartificial muscle constructs is well known in the art (See, e.g. Lu et al).

Naughton et al teach additional cells can be added to form the three-dimensional tissue, including endothelial cells (See Naughton et al, Pg. 3, paragraph 0038). It would have been obvious to one of ordinary skill in the art to additionally include endothelial cells, particularly vascular endothelial cells, in the three-dimensional tissue construct of Naughton et al because at the time the invention was made, inclusion of vascular endothelial cells, in addition to stromal/parenchymal cells, in tissue engineered constructs was known to promote formation of a primitive vascular system (See Atala, col. 2, ln 19-52). Thus, because one of the goals of the tissue construct of Naughton et al is to promote vascularization in the tissue construct, one would be motivated to include the vascular endothelial cells which were known to promote such vasculogenesis (See Naughton et al, Pg. 1, paragraph 0007). Thereby, upon implantation of the tissue construct, Naughton et al effectively co-administers both the stromal cells, which may comprise myoblasts and other tissue specific cells, as well as vascular endothelial cells.

Finally, Naughton et al further teach cells which have been genetically-engineered so as to produce exogenous gene products that promote tissue growth and angiogenesis are desirable for use in the tissue construct; particularly desirable are cells engineered to express vascular endothelial growth factor (VEGF) (See Naughton et al, Pg. 5, paragraphs 0046-0050). While Naughton et al does not provide details on the transfection of the cells with VEGF, at the time the invention was made, means of transfecting cells, including myoblasts, with plasmids encoding VEGF were known in the art. See, for example, Penn et al. Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical. Thus, based on the teachings of Penn et al, it would have been well within the purview of one of ordinary skill in the art to successfully transfect the myoblasts with a plasmid encoding VEGF prior to culturing the myoblasts on the tissue construct of Naughton et al. Still further, it would have been obvious to one skilled in the art to transfect either the endothelial cells or the myoblasts for seeding onto

the tissue construct of Naughton et al. One skilled in the art would have been motivated to transiently transfect either cell population because transient expression by either cell population would result in the presence of VEGF, which is taught to enhance cell growth (See Naughton et al, Pg. 5, paragraph 0050) and to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045).

Thus, based on the teachings described above, it would have been obvious to one of ordinary skill in the art to create a three-dimensional tissue construct for the augmentation of cardiac tissue damaged by ischemia by culturing a first population of myoblasts and a second population of vascular endothelial cells on a three-dimensional tissue scaffold (matrix), wherein at least one of the cell populations has been transfected with a plasmid encoding for VEGF, and implanting the complete tissue construct at a cardiac tissue site that exhibits ischemic damage, thereby inducing assimilation and differentiation of cells and augmenting organ function. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651